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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,752	10/30/2001	Ramy Lidor-Hadas	1662/55002	8981

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EXAMINER	
OH, TAYLOR V	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,752	LIDOR-HADAS ET AL.	
	Examiner	Art Unit	
	Taylor Victor Oh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-8 and 10-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8 and 10-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments with respect to claims 5-8 and 10-93 have been considered but are moot in view of the new ground(s) of rejection.

The Status of Claims

Claims 5-8 and 10-93 are pending.

Claims 5-8 and 10-93 have been rejected.

DETAILED ACTION

Priority

1. It is noted that the application claims benefit of 60/244,283 (10/30/2000), 60/253,819(11/29/2000), and 60/265,539 (01/31/2001).

Drawings

2. The drawings filed on 10/30/2001 are accepted by the examiner.

Claim Objections

Claims 5-8 and 10-18 are objected to because of the following informalities:

In claims 5-8, claims are dependent upon the canceled claim 1. This is improper;

In claims 10-18, claims are dependent upon the canceled claim 9. This is improper. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 40, 42, 44, 71, 89-91 and 93 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims 23, 40, 42, 44, 71, 89-91 and 93 are directed to a pharmaceutical composition comprising the polymorphic various forms of ondansetron hydrochloride. According to the specification, there are some remarks about various polymorphic forms of the ondansetron hydrochloride, but there are no other information about which polymorphic form in the pharmaceutical composition is effective regarding its bioavailability . It is not uncommon to find several polymorphs of compounds existing under normal handling conditions. Just as every polymorph has its own chacteristic X-ray patterns, so does every solvate. Many different polymorphs and /or solvates show varying dissolution rates. Therefore, on the time scale of the pharmaceutical bioavailability, different total amounts of drug are dissolved, resulting in potential bio-

inequivalence of the several forms of the drug. Since these aspects are absent in the specification, the skilled artisan in the art is unable to determine which polymorphic form of ondansetron hydrochloride is suitable for the pharmaceutical composition with respect to the pharmaceutical bioavailability. Therefore, an appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45, 66, and 92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 45 and 66, the claims are directed to the anhydrous ondansetron hydrochloride compound ,but it contains water. This is vague and indefinite because the compound claims are written as if the composition claims. Therefore, an appropriate correction is required.

In claim 92 , the phrase " a therapeutically effective amount" is recited. The expression is vague and indefinite because the claim does not specify how much of the pharmaceutical composition corresponds to the therapeutically effective amount . Therefore, an appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19-23,39-45, 49-50, 52, 57-58, 62-67, 71, 74-76 , 87-91, and 93 are rejected under 35 U.S.C. 102(b) as being anticipated clearly by Wu Gousheng et al (CN 1113234).

Wu Gousheng et al discloses a 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride monohydrate compound (see page 8 on its translation ,lines 6-24); furthermore, an organic base and standard physiological salt and solvate can be incorporated into the compound in order to be used as a medication for treating nausea and vomiting (see abstract). Furthermore, concerning X-ray diffraction patterns and the range of particle size , they are inherently present in the compound and also naturally obtained as unique characteristics for evaluating the compound, not as the novelty of the invention. Moreover, it is not uncommon to find several polymorphs of compounds existing under normal handling conditions. Just as every polymorph has its own characteristic X-ray patterns, so does every solvate.

This compound is identical with the claims.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 5-8, 10-20, 23-48, 51, 53-56, 59-65, and 68-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu Gousheng et al (CN 1113234).

Wu Gousheng et al discloses a 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride monohydrate compound (see page 16 on its translation ,lines 20-22); furthermore, an organic base and standard physiological salt and solvate can be incorporated into the compound in order to be used as a medication for treating nausea and vomiting (see abstract). Concerning the production of the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound, the following steps can be used:

1. dissolving the compound of 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole in 5 ml of ethanol;
2. blowing dry HCl into the solution;
3. cooling down the resultant mixture, crystallizing the compound , and recrystallizing it with water , thereby obtaining the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound (see page 21 , lines 8-17).

Furthermore, in order to isolate the 1,1,2,2,3- pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride monohydrate compound, the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride dihydrate compound is recrystallized with water and dried in a drier containing P_2O_5 (see page 17 , lines 16-17).

Moreover, there is a general procedure for producing the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole

hydrochloride with an aqueous solvent by dissolving the 1,1,2,2,3- pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole to a water /alcohol solvent and adding hydrogen chloride (1N) to the resultant mixture to produce the desired compound (see page 8 , lines 19-24).

However, Wu Gousheng et al differs from the instant invention in that a solvent system contains chloroform, toluene, ketone ,xylene, isopropanol, methyl tert-butyl ether during the process; the exposure is for a period of three weeks or less or 30 to 70 hours; the temperature is from -15^0 C to room temperature; and the mechanical agitation is sonification.

Concerning the use of the various solvent system for producing the desired compound, the reference is silent about them. However, the Wu Gousheng et al does indicate the use of benzene and n-propanol, which are similar to the functionality of the claimed solvents. Therefore, there is no patentable weight over the prior art reference in the absence of an unexpected result using the claimed solvent system.

With respect to the exposing period of three weeks or less or 30 to 70 hours and the temperature is from -15^0 C to room temperature, the limitation of a process with respect to ranges of pH, time and temperature does not impart patentability to a process when such values are those which would be determined by one of ordinary skill in the art in achieving optimum operation of the process. Temperature and period are well understood by those of ordinary skill in the art to be a result-effective variable, especially when attempting to control selectivity of a chemical process.

Regarding the use of the mechanical agitation by a sonic vibration, this is directly related to mechanical expediency. Therefore, it would have been obvious to the skilled artisan in the art to have motivated to employ the sonic vibration as mechanical expediency in order to accelerate the process.

Wu Gousheng et al does teach the general procedure for producing the 1,1,2,2,3-pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole hydrochloride with an aqueous solvent by dissolving the 1,1,2,2,3- pentahydrogen-9-methyl-3((2'-methyl-imidazole-1)-methyl)-4-oxocarbazole to a water /alcohol solvent and adding hydrogen chloride (1N) to the resultant mixture to produce the desired compound. Furthermore, in order to optimize the reaction conditions such as time and temperature for the process, it would have been obvious to the skilled artisan in the art to have motivated to modify the period and temperature to the claimed parameters by routine experimentation, thereby accelerating the reaction process.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tsang Cecilia can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

7/23/07

Cecilia J. Tsang
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